UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/902,572	07/10/2001	Avi Ashkenazi	GNE.1618P2C40	5445

9157 7590 11/21/2003

GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/902,572	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 4/11/02
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____. 5/23/03
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 5/27/03, in which changes were made to the specification (e.g. to remove hyperlinks and complete biological deposit information), and in which claim 39 was amended to include the information specified by claim 44. Claim 44 was cancelled by the amendment. Claims 39-43 are pending in the instant application. This action is FINAL.

Information Disclosure Statement (IDS)

The references cited in the information disclosure statement filed 04-11-02 as Paper No. 3 have been located and considered. The signed and initialed PTO Form 1449 has been mailed with this action.

Receipt is also acknowledged of a supplemental IDS filed on 5/27/03. Only the three references cited on the PTO Form 1449 that are present in the file were actually considered. If applicants wish the other references to be considered, it will be necessary to file an additional IDS along with the cited references.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 39-44 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. **This**

rejection is maintained for reasons of record in Paper No. 13, mailed 2/26/03 and repeated below.

Each of the claims is directed towards an antibody that binds to the polypeptide described by SEQ ID NO: 255. The antibody can be a fragment that binds to SEQ ID NO: 255. The antibody can be a monoclonal antibody. The antibody can be labeled. The antibody can be humanized. The antibody can "specifically" bind to the polypeptide shown in SEQ ID NO: 255. Any utility for the claimed antibodies must be specific and substantial, or well established, for the protein encoded by SEQ ID NO: 255. Utilities simply directed to detection of, or purification of, the protein described by SEQ ID NO: 255 cannot be considered as substantial (i.e. having a "real-world" use) in the absence of a specific and substantial, or well-established utility for the protein to which the antibody binds. No such specific and substantial or well-established utility has been described for the protein described by SEQ ID NO: 255.

SEQ ID NO: 255 appears to have been novel in the art at the time of filing. Likewise, the nucleic acid sequence disclosed by applicants as encoding SEQ ID NO: 255, SEQ ID NO: 254, likewise appears to be novel in the art. Therefore, there is no well-established utility for the disclosed protein or antibodies specific for the protein.

The specification asserts that, based upon BLAST and FastA sequence analysis, various portions of PRO302 have significant homology with various protease proteins (page 110, top paragraph). Exactly which portions have homology to which portions of which other known proteases is not taught, however. Based upon the assertion that PRO302 comprises proteolytic activity, the specification asserts that PRO302 has utility in vivo for therapy as well as in vitro utilities. There is no indication in the specification that the supposed protease has any *specific*

target for its supposed activity (e.g. association with a particular disease or specific substrate). There is no specific disease or condition shown in the prior art or instant specification to be associated with the protein described by SEQ ID NO: 255.

It is not likely that one of skill in the art could reasonably predict based upon the primary sequence of SEQ ID NO: 255 what specific activity PRO302 may have. The relationship between the sequence of a protein and its tertiary structure (in essence the structure which defines its activity), is not well understood and is not predictable as evidenced by Berendsen (Science. 1998, Vol. 282, pages 642-643; see the entire document). This reference teaches that "Thus, one of the "grand challenges" of high-performance computer-predicting the structure of proteins-acquires much of the flavor of the Holy Grail quest of the legendary knights of King Arthur: It is extremely desirable to possess but extremely elusive to obtain." (Page 643, columns 1-2). The whole reference teaches about the unpredictability in the art concerning protein structure, and failures to make it predictable. Thus, as taught by Berendsen, it is unlikely that one could predict the structural/functional characteristics of PRO302 based upon primary sequence alone. Further supporting Berendsen's teachings, Galparin et al (Nature Biotechnology, Vol. 18, pages 609-613, June 2000; see the entire reference) teach that "sequence comparison methods, even the best ones, are of little help when a protein has no homologs in current databases or when all database hits are to uncharacterized gene products." Galperin et al disclose that "assessing the actual power of the context based method for protein function prediction requires extensive testing by labor-consuming, case-by-case, computational, and eventually experimental analysis." Attwood (Science, Vol. 290, pages 471-473, see the entire reference) also states that it is presumptuous to make functional assignments merely on the basis

of some degree of similarity between sequences." It is clear from the cited references that one cannot reliably predict based upon primary structure alone or on mere sequence homology what specific activity PRO302 might possess.

The specification does teach in Example 85 that the PRO302 protein has an effect on vascular leakage when injected into hairless guinea pigs. While the specification concludes that PRO302 protein can induce vascular permeability in the guinea pig model, it does not give the actual data or an indication of the relative activity of the PRO302 protein compared to the positive control. In addition to not providing a basis for one of skill in the art to determine the actual effectiveness of PRO302 in inducing vascular permeability, the specification does not provide a basis to envision a specific, real-world application for the asserted ability to induce vascular permeability. Based on these teachings, one of skill in the art at the time of applicants' invention would not be able to recognize a specific utility (e.g. specific proteolytic substrate) or substantial utility (i.e. not requiring additional research in order to confirm a real-world application for the claimed proteins) for the claimed proteins. Because no specific and substantial or well-established utility has been demonstrated for the protein described by SEQ ID NO: 255, one of skill in the art would not have been able to recognize a specific and established utility for the claimed antibodies.

Claims 39-44 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Response to Arguments

Applicant's arguments filed on 5/27/03 have been fully considered but they are not persuasive. The response essentially argues: 1) the patent office is not the FDA and should not apply its standards, 2) the assertion that the claimed invention is useful is credible, 3) the results of the vascular leak assay of Example 85 are sufficient to establish a specific, substantial and credible utility for the protein to which the claimed antibodies bind (i.e. PRO302 described by SEQ ID NO: 255), 4) PRO302 was demonstrated to increase skin vascular permeability, 5) such assays are known and used in the art to correlate such activity with disease and/or evaluate the vascular permeabilizing function of a given substance (e.g. the Wei et al, Wise et al and Collins et al references), 5) vascular permeabilization can occur during wound healing or in pathological conditions such as tumor formation, 6) just as VPF (alternatively known as VEGF; see the Collins et al reference) has been shown to play a role in many important biological functions, a variety of real-life utilities are envisioned for PRO302 base on the results of Example 85 (e.g. PRO302 could be used to induce wound healing), 7) antibodies raised against PRO302 could be used to diagnose target tissue disorders (e.g. tumor formation), 8) working Example 85 provides a positive control (human VEGF) and PRO302 tested positive in the assay (i.e. response greater than 5-7 mm in diameter), 9) the fact that other proteins may induce such a response is irrelevant for utility considerations, 10) applicants' assertion that PRO302 is an inducer of vascular permeability would be recognized by the skilled artisan as a credible assertion.

At no point in making the rejection did the examiner state that applicants' assertions concerning any utility for PRO302 were not credible (e.g. in the sense of claiming a perpetual motion machine). Rather, the grounds for the rejection are made along the lines of a lack of a

specific and substantial utility. The results Example 85 do not support a specific or substantial utility. No specific disease or condition was shown to be correlated with the presence and/or expression of PRO302. Nor has it been shown that PRO302 has any effect, naturally or otherwise, on wound healing. The mere fact that PRO302 may have an effect on vascular permeabilization is not sufficient grounds for one of skill in the art to assume that it can be used in wound healing and/or diagnosis of a particular disease or condition. Moreover, the examiner cannot determine the *degree* to which PRO302 had any affect on vascular permeabilization. For example, while it is true that applicants did provide a "positive control" of sorts for Example 85 by using VEGF (producing a response of 15-23 mm), the statement that PRO302 tested positive merely means that, by applicants' standards, PRO302 produced a response of >5-7 mm depending on the assay. The exact degree of response observed (e.g. as compared to VEGF) is not described in the specification, making it difficult to determine just how effective PRO302 is at inducing permeability. Neither applicants' response nor the references cited in their response indicate that PRO302 would necessarily have the asserted utilities. The skilled artisan would reasonably have concluded at the time of filing that the claimed invention lacks a specific (i.e. particular proteolytic substrate, or correlation to a particular disease or condition) or substantial (i.e. not requiring additional experimentation to identify and confirm a real world use) utility.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 39-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is a new rejection in that it has been shifted to claims 39-43 in response to applicants' amendment of the claims in the response filed 5/27/03. The grounds for the rejection are maintained for reasons of record in Paper No. 13, mailed 2/26/03 and repeated below.**

Claim 44 is vague and indefinite in that the metes and bounds of the words "specifically binds to" are unclear. The phrase does not appear to be explicitly defined in the specification and makes it unclear the nature and degree of the characteristics required for an antibody to bind "specifically" to a given protein. Does the phrase mean that the antibody only binds to the recited PRO32 protein and no other proteins? Does it refer to the strength of binding? Does the phrase mean that the antibody only binds a few other proteins? It would be remedial to amend the claim language to explicitly set forth the nature and degree of the characteristics required for the claimed antibody to bind "specifically" a given protein.

Response to Arguments

Applicants' arguments filed on 5/27/03 have been fully considered but they are not persuasive. The response essentially argues: the term "specifically binds to" embraces an art-recognized concept where an antibody binds to a particular antigen and does not significantly cross-react with other antigens. Applicants' assertion is unsupported. Applicants are welcome to provide teachings from the prior art to support their argument. In the meantime, it is not clear the degree of antigenic cross-reaction that would satisfy the limitation of "significant" cross-reaction.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

GERRY LEFFERS
PRIMARY EXAMINER

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

Ggl